The enablement requirement of § 112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention without undue experimentation. *In re Wand*s, 8 USPQ2d 1400 (Fed. Cir. 1988).

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wand*s, 8 USPQ2d at 1404.

Applicants assert that considering the state and the predictability of the prior art, the specific guidance in the specification, the presence of working examples in the specification, and the limited quantity of experimentation needed to make or use the invention based on the content of the disclosure, one skilled in the art would be able to practice the claimed invention without undue experimentation.

The specification describes the state and predictability of the prior art for mass spectroscopy in detail and indicates that the state of the art is well established. The specification describes the state of the art for electron spray ionization mass spectroscopy as useful for studying the interactions of very high molecular weight biopolymers such as proteins and nucleic acids greater than 10 kDa in mass. See, for example, pages 17 to 29 of the specification. The mass spectrometer can be used to identify compounds, i.e., ligands, from the set of compounds that are "weak" binders with respect to the target molecule. See, for example, page 29, l. 14 to page 30, line 22. Furthermore detailed instructions within the specification describe the set-up and optimization of the mass spectrometer for measuring ligand binding to target molecules. See page 52, line 1 to page 54, line 25.

Applicants assert that the specification describes how one skilled in the art would differentiate binding of test compounds to a target molecule where binding is, for example, competitive, concurrent, cooperative or non-competitive. See specification, for example, page 36, l. 17 to page 37, l. 6. The Office is incorrect in stating that "the predictability of detecting the binding of a test compound to a target molecule [by mass spectroscopy] by the displacement of a 'standard compound' with no limitation that the test and 'standard' compounds bind the same sites on the target molecule is very low, particularly with larger target molecules and smaller test

molecules." See Advisory Action, paragraph 3. Moreover, Applicants agree with an earlier statement by the Office that "competitive and non-competitive binders would provide different results as compared to the same standard molecule." See May 7, 2002 Office Action (Paper No. 13), page 4. Applicants agree that the results would be different. Moreover one of ordinary skill in the art would be able to ascertain the binding nature of the several test compounds to the target molecule. The very nature of mass spectroscopy as taught in the specification allows one to differentiate between binding that is, for example, competitive, concurrent, cooperative, or non-competitive. The specification describes, in detail, identification of ligands having selected binding characteristics and probing the structure activity relationship using mass spectrometry. See specification, for example, page 29, l. 14 to page 30, l. 15.

Contrary to the Office's assertion, the specification provides detailed guidance with respect to selection of "standard" compounds and provides detailed guidance with respect to selecting different types of "standard" compounds for use with different types of target molecules. The specification further provides guidance on how to select "standard" compounds that are detectable by mass spectrometry and able to bind a target molecule.

Applicants assert that the specification teaches, for example, the use of ammonium or some other amine as the standard compound conforming with the teaching of one skilled in the art. One would know that simple amines will bind to biological binding sites with at least a weak affinity. The displacement of the amines by another test compound demonstrates that the test compound has a greater affinity for the ligand than, at least, ammonium.

When the "standard" compound does not bind to the target molecule, one is informed thereby that the target does not present binding pockets having an affinity for that chemical type of "standard" compound. The present application teaches the use of various classes of standard compounds to assist in the selection of a proper standard compound. The presently claimed invention is directed to methods related to selecting those members of a group of compounds that can form a non-covalent complex with a target molecule, and provides significant guidance for practicing the claimed invention.

The specification teaches one of ordinary skill in the art to use an amine such as ammonium to ascertain two important attributes of the target molecule. The method is useful to

determine whether an amine-like "standard" compound will bind to the target molecule and, if so, at what binding strength. Where the target is RNA or DNA, the use of nitrogen heterocycles is recommended in addition to various ammonium salts, for example, such as ammonium acetate. See specification, for example, page 34.

The specification provides sufficiently detailed description to enable a person skilled in the art to practice the claimed method without undue experimentation. The specification describes, in detail, a broad range of exemplary compounds/ligands and target molecules known in the art. The standard compounds/ligands are useful to bind a broad range of target molecules, *e.g.*, RNA, DNA or protein target molecules. See, for example, page 31, line18 to page 33, line 21. The specification describes sub-sets of groups of compounds that are useful in the claimed invention. The specification describes groups of compounds that are ligands, derivatized ligands, or concatenated ligands that bind to the target molecules. See for example, page 35, line 23 to page 40, line 17. Ligands may bind competitively, concurrently or mixed binding to the target molecule. See for example, page 40, line 5 to page 46, line 9. Using the claimed method, one may identify by mass spectrometric analysis the members of the sub-set that form complexes with the target by discerning signals arising from the members complexed with the target and identifying the members by the respective molecular mass or other physical property.

The specification provides working examples of the claimed invention, that is, a method of selecting those members of a group of compounds that can form a non-covalent complex with a target molecule. See, for example , page 47, line 13 to page 48, line 24; and Examples 4 and 5, Figures 6, 7, and 8. An example is provided that demonstrates the binding of amide compounds to 16S ribosomal RNA, comparing the binding of two ligands to a concatenated compound of the two ligands. Figures 6, 7, and 8 provide mass spectrographic analysis using methods of the presently claimed invention.

> "...a [mass spectrographic] analysis of a library of amide compounds revealed two [compounds] having binding affinity for a fragment of bacterial 16S ribosomal RNA. The two ligands (IBIS-271583 and IBIS-326611) both incorporated a piperazine moiety and a concatenated compound of the two ligands was prepared having a common piperazine moiety from which the remainder of the ligand structures depend. The concatenated compound (IBIS-326645) is shown in figure 8 to bind the target 16S RNA fragment with greater affinity

(52.4% of the target) than either of the two parent ligands in figures 6 and 7 (27.8% and 14.7% respectively)."
See specification, page 48, lines 7 to 18.

The description in the specification is sufficient to enable one skilled in the art to practice the breadth of the claims. The specification describes, in detail, exemplary compounds/ligands and target molecules known in the art. The specification provides a detailed list of standard compounds/ligands that are useful to bind a variety of target molecules, for example, RNA, DNA or protein. The operating performance conditions of the mass spectrometer are adjusted according to the binding affinity between the standard ligand and the target molecule, which may be RNA, DNA, or protein. See, for example, page 34, line 13 to page 35, line 8.

The claims are fully enabled; one is fully informed of how to practice methods for selecting those members of a group of compounds that can form a non-covalent complex with a target molecule. Applicants assert that considering the state and the predictability of the prior art, the specific guidance in the specification, the presence of working examples in the specification, and the limited quantity of experimentation needed to make or use the invention based on the content of the disclosure, one skilled in the art would be able to practice the claimed invention without undue experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 112, first paragraph.

**35 U.S.C. § 112 second paragraph**

Claims 33 and 35 are rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are rejected over the allegedly unclear terms of "diverse" and "related." Applicants respectfully traverse the rejection because the claims are clear and definite within the patent laws.

Applicants submit that the Office mistakenly concludes that the claims are indefinite since these terms are terms of degree, and the specification allegedly does not provide a standard for determining degree. As stated in Applicants' previous response, just because a claim includes a term of degree does not automatically render the claim indefinite. *Seattle Box Co., v.*

*Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 U.S.P.Q. 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification. *See* M.P.E.P. § 2173.05(b). Applicants submits that these terms do not render the claims indefinite, and one skilled in the art would have no difficulty in determining the metes and bounds of the claims that contained such terms.

Nonetheless, without acceding to the Office's argument, Applicants have cancelled claim 33 and amended claims 34 and 35 to clarify the claimed invention. In view of the above discussion, the claims set forth the subject matter that Applicants regard as the invention. Applicants assert that the metes and bounds of the claims are well defined. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 112, second paragraph.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

Date: November 4, 2002

**Phillip A. Singer**
**Registration No. 40,176**

**John W. Caldwell**
**Registration No. 28,937**

WOODCOCK WASHBURN LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**In the Claims:**

Claim 33 has been cancelled without prejudice to presentation of the claim in a continuing application.

Claims 34 and 35 have been amended as follows.

30. A method of selecting those members of a group of compounds that can form a non-covalent complex with a target molecule comprising:

selecting a mass spectrometer;

selecting a standard compound that forms a non-covalent binding complex with said target molecule, said non-covalent binding complex having a baseline affinity;

mixing an amount of said standard compound with an excess amount of said target molecule such that unbound target molecule is present in said mixture;

introducing said mixture of said standard compound and said target molecule into said mass spectrometer;

adjusting the operating performance conditions of said mass spectrometer such that the signal strength of said standard compound bound to said target molecule is from 1% to about 30% of signal strength of unbound target molecule;

introducing a sub-set of said group of compounds into a test mixture of said target molecule and said standard compound;

introducing said test mixture into said mass spectrometer;

identifying the members of said sub-set that form complexes with said target by discerning signals arising from said members complexed with said target and identifying the members by their respective molecular masses.

31. The method of claim 30 wherein said signals are measured as the relative ion abundance.

32. The method of claim 30 wherein said sub-set comprises from about 2 to about 8 member compounds.

34. (Twice Amended) The method of claim [33] 30 wherein said group of compounds comprises a collection library of diverse compounds selected from a historical repository of compounds, a collection of natural products, a collection of drug substances, a collection of intermediates produced in forming drug substances, a collection of dye stuffs, a commercial collection of chemical substances or a combinatorial library of related compounds.

35. (Twice Amended) The method of claim [33] 34 wherein said collection library of diverse compounds comprises a library of compounds having from 2 to about 100,000 members.

36. The method of claim 30 further including storing the relative abundance and stoichiometry of said complexes of said member compounds and said target in a relational database.

37. The method of claim 36 further including cross-indexing said relative abundance and stoichiometry of said complexes to the structures of said member compounds.

38. The method of claim 30 wherein each of the members of said group of compounds, independently, has a molecular mass less than about 1000 Daltons and has fewer than 15 rotatable bonds.

39 The method of claim 30 wherein each of the members of said group of compounds, independently, has a molecular mass less than about 600 Daltons and has fewer than 8 rotatable bonds.

40. The method of claim 30 wherein each of the members of said group of compounds, independently, has a molecular mass less than about 200 Daltons, has fewer than 4 rotatable bonds, or has no more than one sulfur, phosphorous or halogen atom.

41. The method of claim 30 wherein said mass spectrometer is an electrospray mass spectrometer.

42. The method of claim 30 wherein said target molecule is a RNA, a protein, a RNA-DNA duplex, a DNA duplex, a polysaccharide, a phospholipid or a glycolipid.

43. The method of claim 30 wherein said target molecule is RNA.

44. The method of claim 30 wherein said target molecule is RNA and said baseline affinity expressed as a dissociation constant is about 50 millimolar.

45. The method of claim 30 wherein said target molecule is RNA and said standard ligand is ammonium.

46. The method of claim 30 wherein said electrospray mass spectrometer includes a desolvation capillary and a lens element; and

said adjustment of said operating performance conditions includes adjustment of the voltage across said capillary and said lens element.